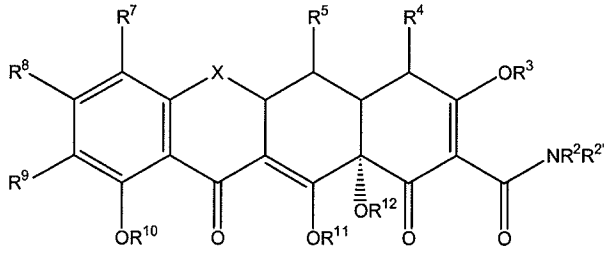
Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^{2}[[,]] and $R^{2'}$~~, $R^{4'}$, and $R^{4''}$~~ are each ~~independently~~ hydrogen~~, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety~~;

$R^{4'}$ and $R^{4''}$ are each alkyl;

R^{4} is $NR^{4'}R^{4''}$~~, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen~~;

R^{3}, R^{11} and R^{12} are each hydrogen~~, or a pro-drug moiety~~;

R^{10} is hydrogen~~, or a prodrug moiety~~;

R^{5} is hydroxyl, hydrogen[[,]] or thiol~~, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy~~;

R^{6} and $R^{6'}$ are independently hydrogen, ~~methylene, absent,~~ hydroxyl, ~~halogen,~~ thiol[[,]] or alkyl~~, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~;

R^{7} is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl[[,]] or substituted or unsubstituted benzothienyl~~, indolyl, or pyrrolyl~~;

R^{9} is hydrogen; and

R^8 is hydrogen~~, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~; and pharmaceutically acceptable salts thereof, such that malaria is treated or prevented in said subject.

2. **(Canceled)**

3. **(Canceled)**

4. **(Currently Amended)** The method of ~~claim 3~~claim 1, wherein R^5, R^6, and $R^{6'}$ are each hydrogen.

5 - 28. **(Canceled)**

29. **(Currently Amended)** The method of claim 1, wherein R^7 is substituted ~~or unsubstituted~~ furanyl[[,]] or thienyl~~, or pyrrolyl~~.

30. **(Previously Presented)** The method of claim 29, wherein R^7 is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, alkenyl, alkynyl, or aryl.

31. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with alkoxy and further wherein said alkoxy is methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.

32. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with alkyl and further wherein said alkyl is substituted or unsubstituted methyl, ethyl, propyl, butyl or pentyl.

33. **(Previously Presented)** The method of claim 32, wherein said substituted methyl, ethyl, propyl, butyl or pentyl is substituted with an amino, carbocyclic or heterocyclic group.

34. **(Currently Amended)** The method of claim 30, wherein R^7 is substituted with acyl and further wherein said acyl is acetyl.

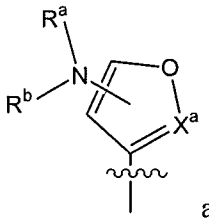
35. **(Currently Amended)** The method of claim 1, wherein R^7 is substituted or unsubstituted benzofuranyl[[,]] or substituted or unsubstituted benzothienyl~~, or indolyl~~.

36. **(Currently Amended)** The method of claim 1, wherein R^7 is unsubstituted thienyl~~, pyrrolyl,~~ or unsubstituted furanyl.

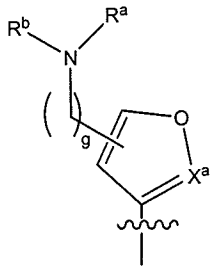
37 – 41. **(Canceled)**

42. **(Currently Amended)** The method of ~~claim 1~~claim 29, wherein ~~R^7~~said substituent comprises an ionizable nitrogen atom.

43. **(Previously Presented)** The method of claim 1, wherein R^7 is selected from the group consisting of:



and



wherein:

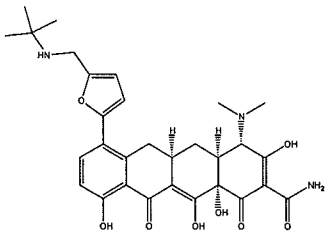
R^a and R^b are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; and

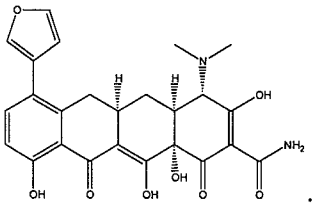
X^a is substituted carbon.

44 – 48. **(Canceled)**

49. **(Previously Presented)** The method of claim 1, wherein said compound is selected from the group consisting of:



and



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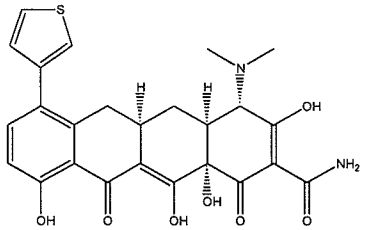
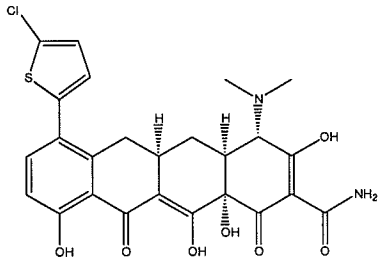
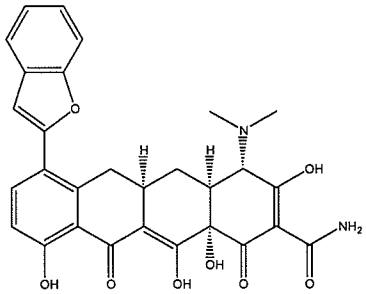
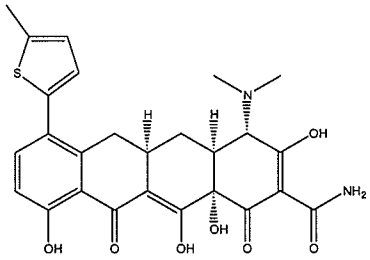
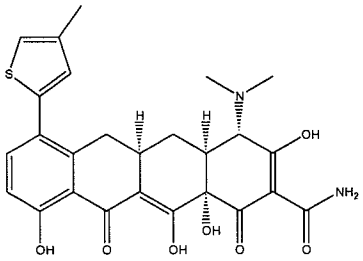
50. **(Currently Amended)** The method of claim 1, wherein said compound is selected from the group consisting of:

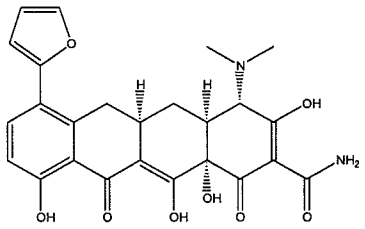


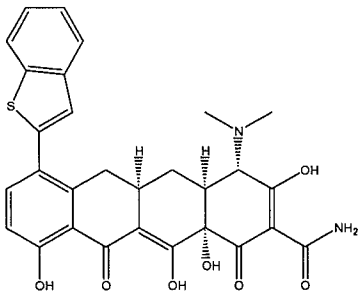


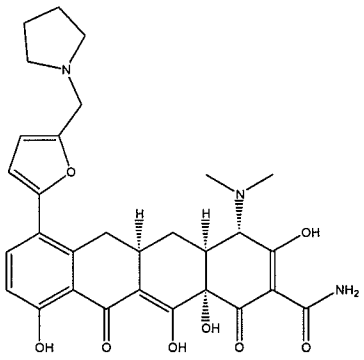


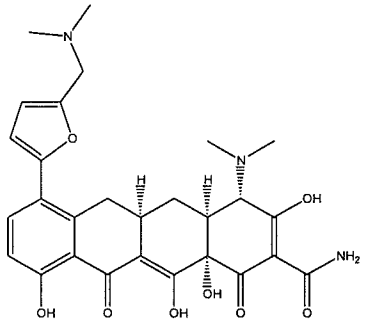


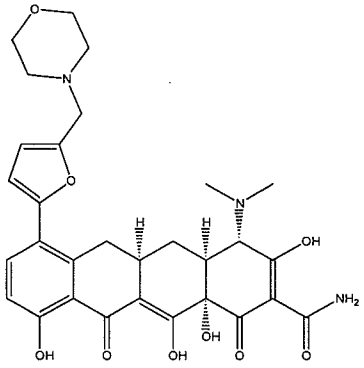


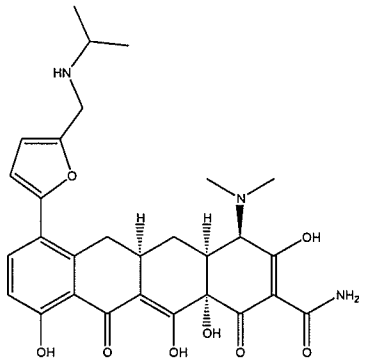


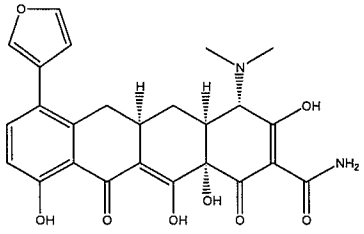


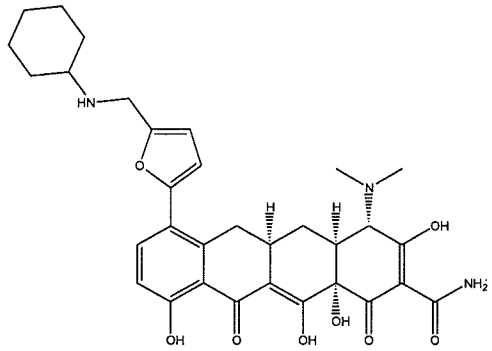


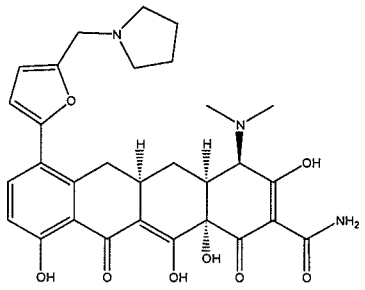


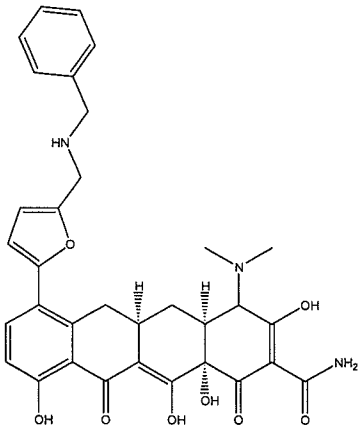


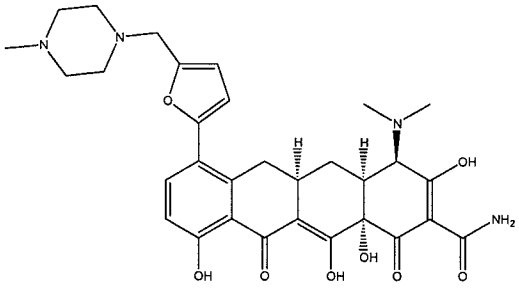


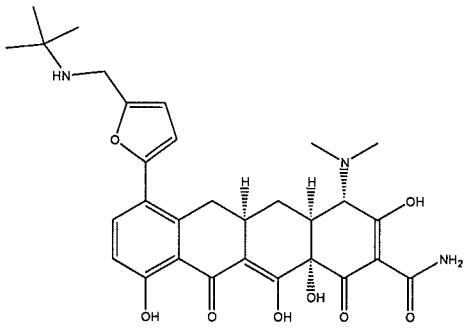


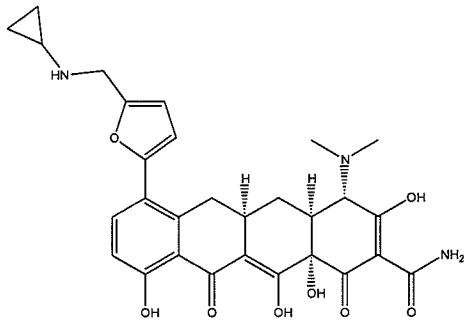


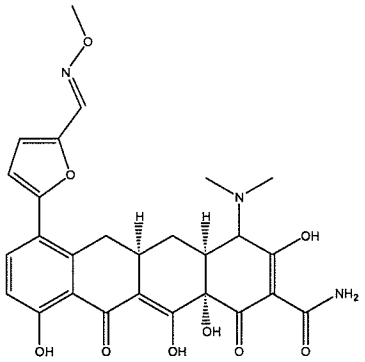


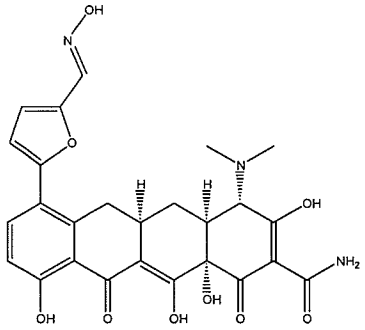


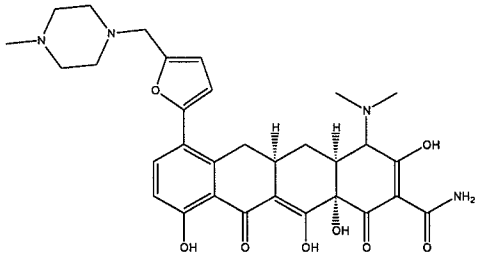


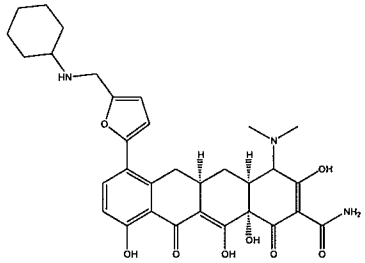


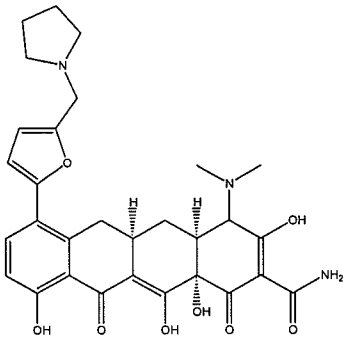


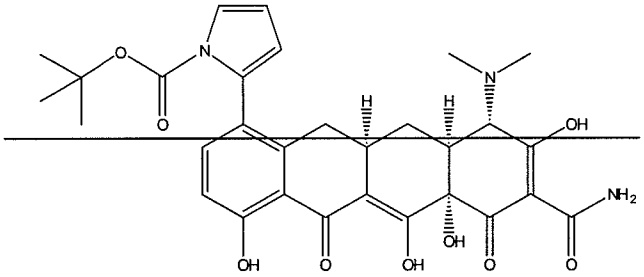


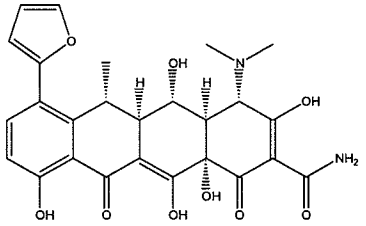


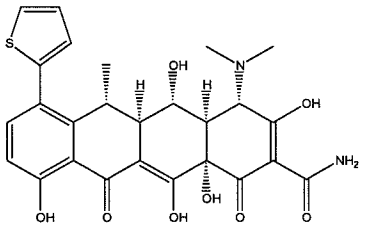


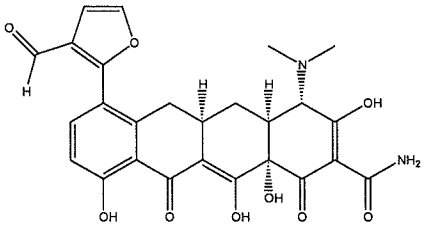


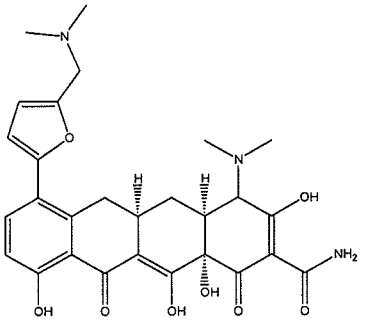


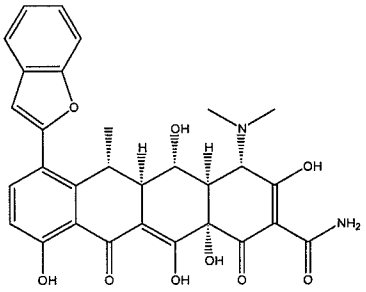


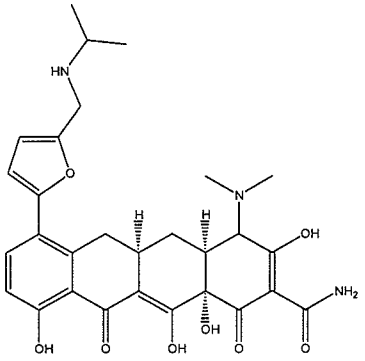


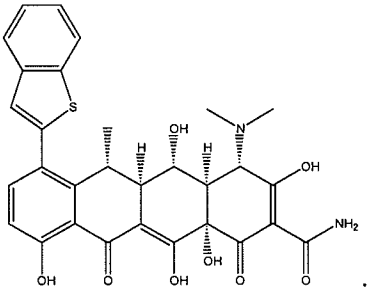












and .

51. **(Original)** The method of claim 1, wherein said subject is a human.

52. **(Currently Amended)** The method of claim 1, wherein said substituted tetracycline compound ~~is~~ has anti-gram positive microbial ~~gram positive~~ activity.

53. **(Currently Amended)** The method of claim 52, wherein said anti-gram positive microbial ~~gram positive~~ activity is greater than about 0.05 μg/ml.

54. **(Currently Amended)** The method of claim 53, wherein said anti-gram positive microbial ~~gram positive~~ activity is greater than about 5 μg/ml.

55. **(Currently Amended)** The method of claim 1, wherein said substituted tetracycline compound ~~in~~is non-antibacterial.

56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25 μg/ml or greater.

57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

60. **(Currently Amended)** The method of claim 59, wherein said substituted tetracycline compound has [[an]]a MIC or 5 nM or less.

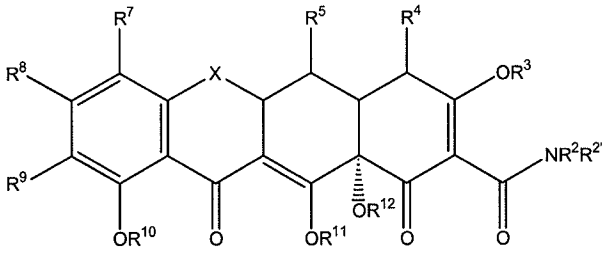
61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.

62. **(Currently Amended)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, ~~proguanil,~~ and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.

63 – 65. **(Canceled)**

66. **(Previously Presented)** The method of claim 1, further comprising administering an anti-malarial compound selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^{2}[[,]] and $R^{2'}$, ~~$R^{4'}$, and $R^{4''}$~~ are each ~~independently~~ hydrogen~~, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety~~;

$R^{4'}$ and $R^{4''}$ are each alkyl;

R^{4} is $NR^{4'}R^{4''}$~~, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen~~;

R^{3}, R^{11} and R^{12} are each hydrogen~~, or a pro-drug moiety~~;

R^{10} is hydrogen~~, or a prodrug moiety~~;

R^{5} is hydroxyl, hydrogen[[,]] or thiol~~, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy~~;

R^{6} and $R^{6'}$ are independently hydrogen, ~~methylene, absent,~~ hydroxyl, ~~halogen,~~ thiol[[,]] or alkyl~~, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~;

R^{7} is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl[[,]] or substituted or unsubstituted benzothienyl~~, indolyl, or pyrrolyl~~;

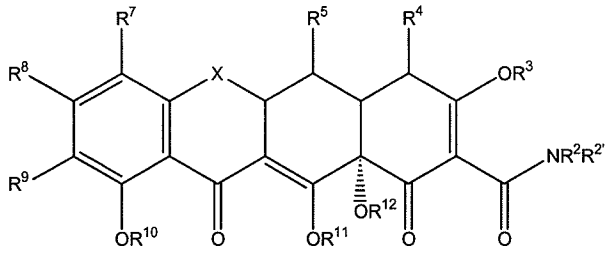
R^{9} is hydrogen; and

R^{8} is hydrogen~~, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~; and pharmaceutically acceptable salts thereof.

68. **(Original)** The method of claim 67, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin,

arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide, and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^{2}[[,]] and $R^{2'}$~~, $R^{4'}$, and $R^{4''}$~~ are each ~~independently~~ hydrogen~~, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety~~;

$R^{4'}$ and $R^{4''}$ are each alkyl;

R^{4} is $NR^{4'}R^{4''}$~~, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen~~;

R^{3}, R^{11} and R^{12} are each hydrogen~~, or a pro-drug moiety~~;

R^{10} is hydrogen~~, or a prodrug moiety~~;

R^{5} is hydroxyl, hydrogen[[,]] or thiol~~, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy~~;

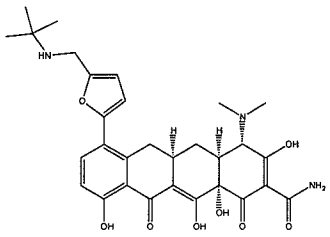
R^{6} and $R^{6'}$ are independently hydrogen, ~~methylene, absent,~~ hydroxyl, ~~halogen,~~ thiol[[,]] or alkyl~~, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~;

R^{7} is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl[[,]] or substituted or unsubstituted benzothienyl~~, indolyl, or pyrrolyl~~;

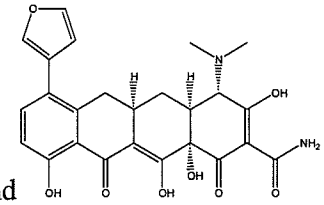
R^{9} is hydrogen; and

R^8 is hydrogen~~, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~; and pharmaceutically acceptable salts thereof.

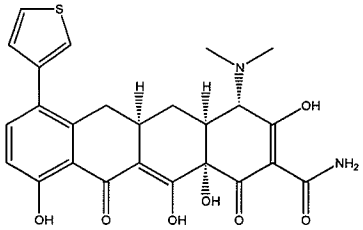
70. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:

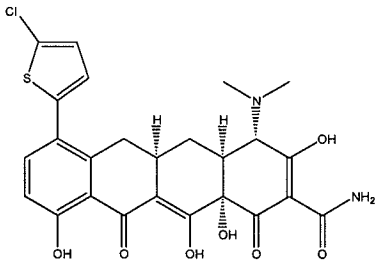


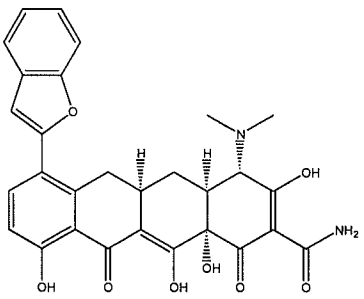
and

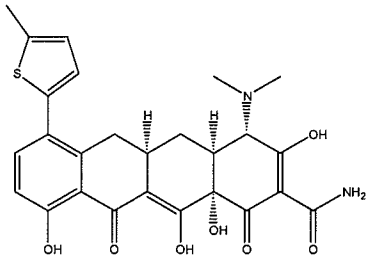


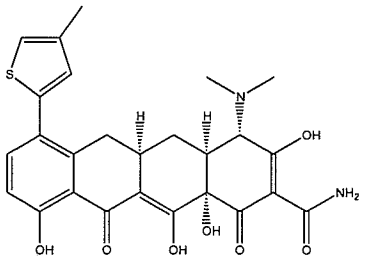
71. **(Currently Amended)** The method of claim ~~67 or~~ 69, wherein said substituted tetracycline compound is selected from the group consisting of:

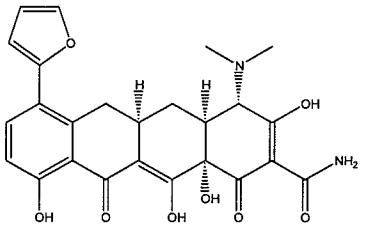


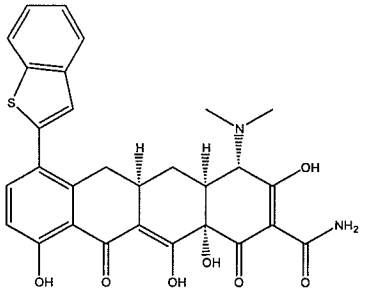


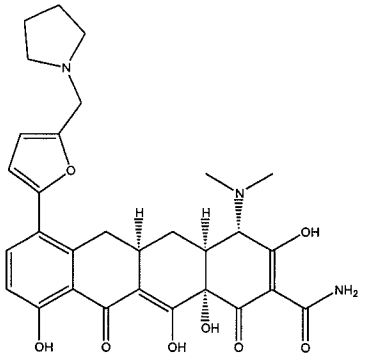


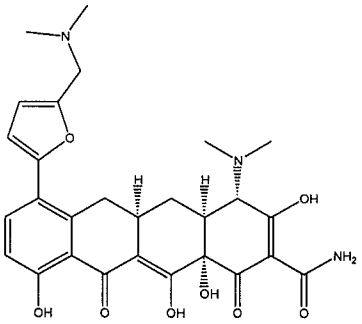


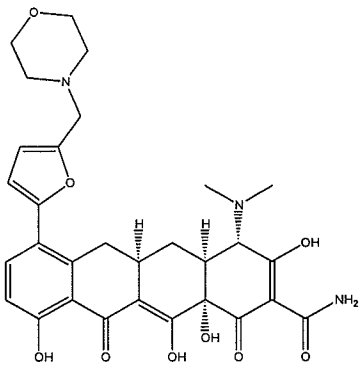


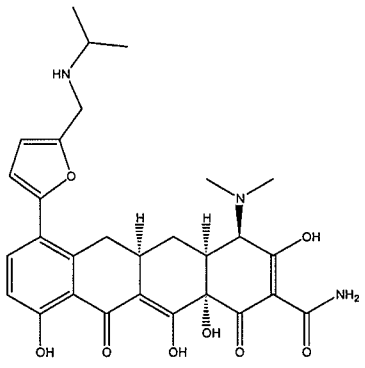


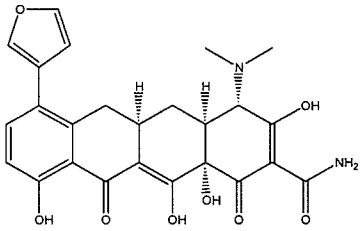


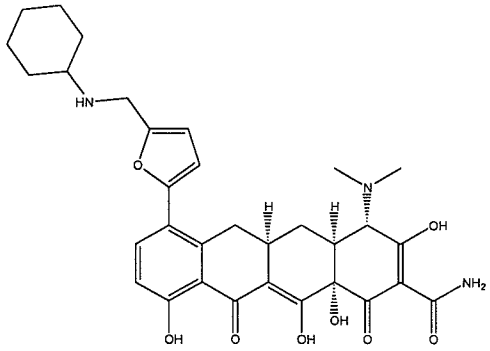


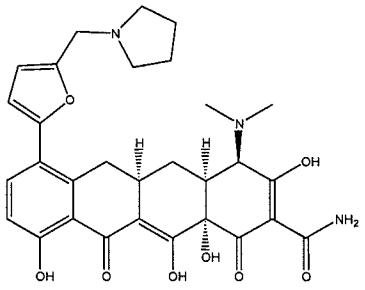


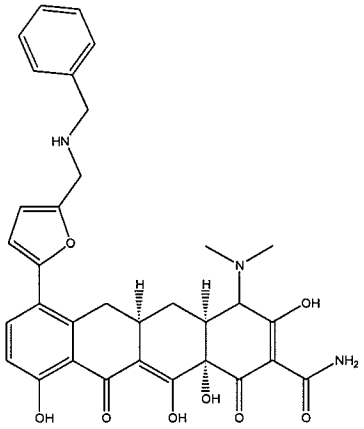


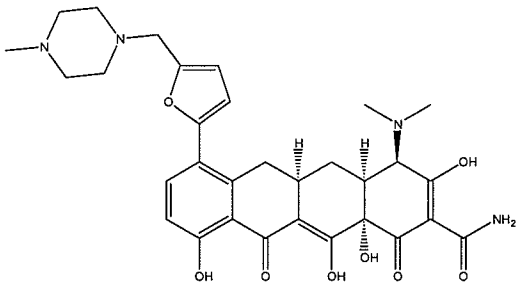


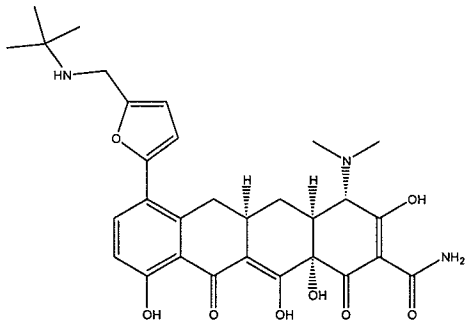


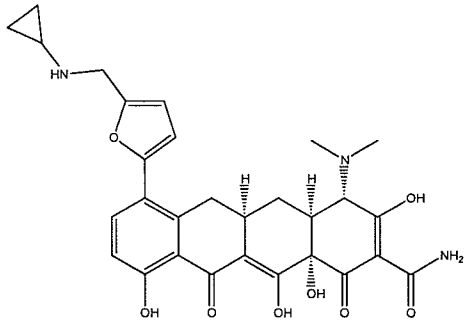


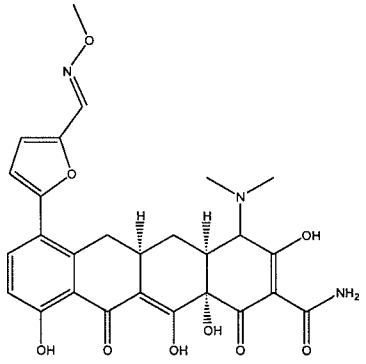


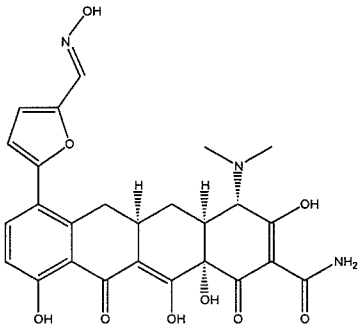


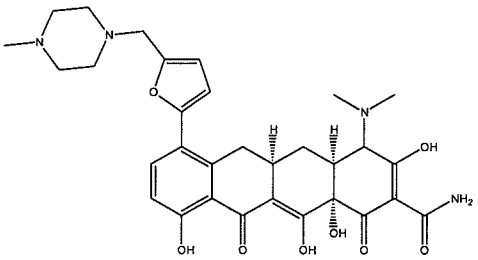


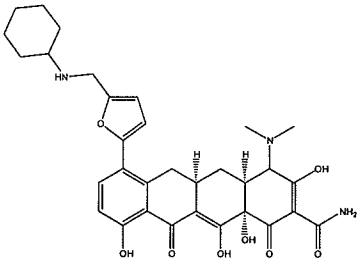


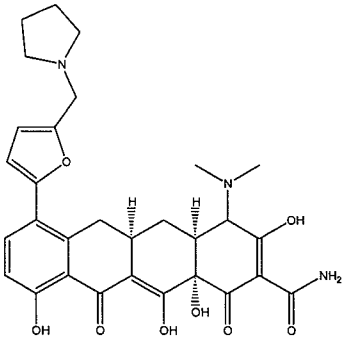


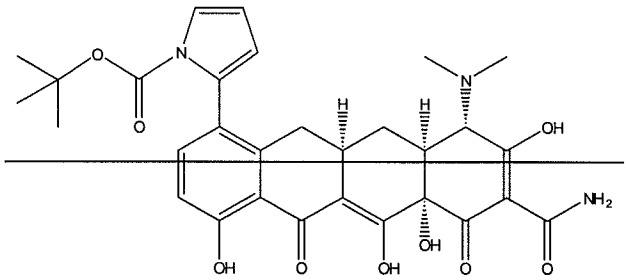


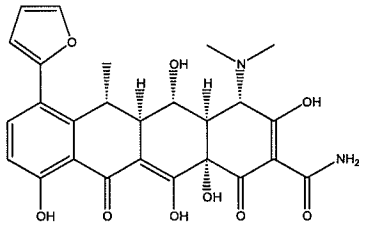


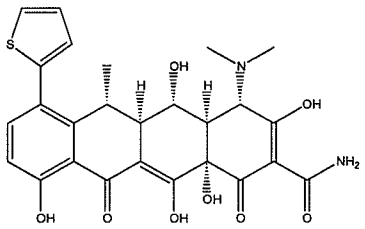


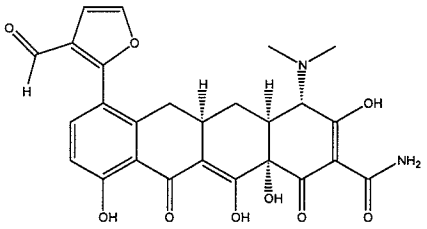


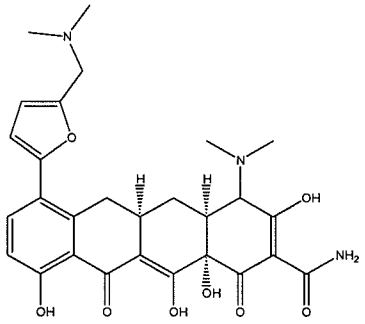


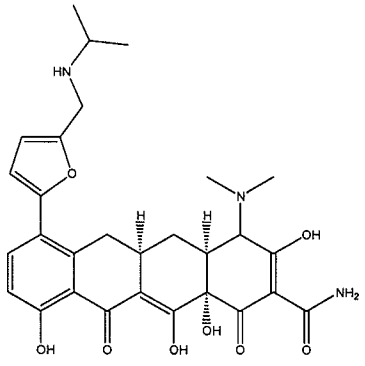


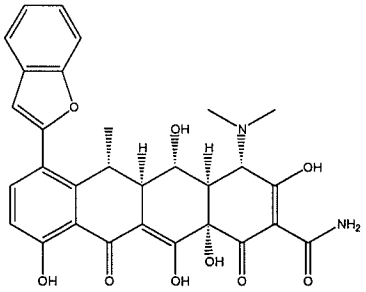


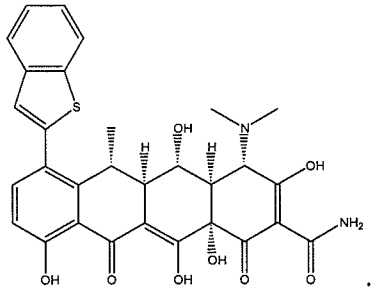










and  .

72. **(Currently Amended)** The method of claim ~~67 or~~ 69, wherein said substituted tetracycline compound is non-antibacterial.

73. **(Currently Amended)** The method of claim ~~67 or~~ 69, wherein said substituted tetracycline compound ~~is~~ has anti-gram positive microbial ~~gram positive~~ activity.

74. **(Currently Amended)** The method of claim 73, wherein said anti-gram positive microbial ~~gram positive~~ activity is greater than about 0.05 μg/ml.

75. **(Currently Amended)** The method of claim 74, wherein said anti-gram positive microbial ~~gram positive~~ activity is greater than about 5 μg/ml.

76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25 μg/ml or greater.

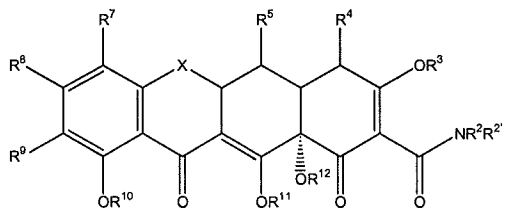
77. **(Currently Amended)** The method of claim ~~67 or~~ 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Currently Amended)** The method of claim 79, wherein said substituted tetracycline compound has [[an]]a MIC or 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CR^{6'}R^{6}$;

R^{2}[[,]] and $R^{2'}$~~, $R^{4'}$, and $R^{4''}$~~ are each ~~independently~~ hydrogen~~, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety~~;

$R^{4'}$ and $R^{4''}$ are each alkyl;

R^{4} is $NR^{4'}R^{4''}$~~, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen~~;

R^{3}, R^{11} and R^{12} are each hydrogen~~, or a pro-drug moiety~~;

R^{10} is hydrogen~~, or a prodrug moiety~~;

R^{5} is hydroxyl, hydrogen[[,]] or thiol~~, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy~~;

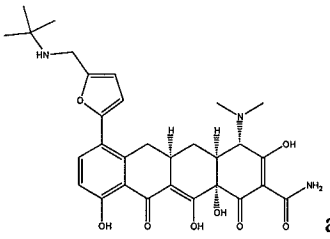
R^{6} and $R^{6'}$ are independently hydrogen~~, methylene, absent,~~ hydroxyl~~, halogen,~~ thiol[[,]] or alkyl~~, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~;

R^{7} is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl[[,]] or substituted or unsubstituted benzothienyl~~, indolyl, or pyrrolyl~~;

R^{9} is hydrogen; and

R^{8} is hydrogen~~, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl~~; and pharmaceutically acceptable salts thereof.

82. **(Previously Presented)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is selected from the group consisting of:



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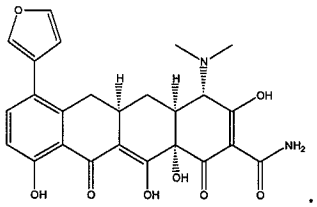

.

83. **(Canceled)**

84. **(Original)** The pharmaceutical composition of claim 81, further comprising a secondary agent.

85. **(Original)** The pharmaceutical composition of claim 84, wherein the secondary agent is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. **(Canceled)**

87. **(Canceled)**